

## REVIEW ARTICLE

## IMPORTANCE OF IMMUNONUTRIENTS

Puja Dullo, Neeraj Vedi\*

Department of Physiology, Government Medical College, Kota, Rajasthan, \*Department of Paediatrics, Dr. Moopens Group, Sohar, Sultanate of Oman

Over last two decades the role of certain nutrients has been found to have pharmacologic effect on immune and inflammatory parameters. The modulation of the activities of the immune activation by nutrients or specific food items fed in amounts above these normally encountered in the diet are defined as Immunonutrients. Few examples are  $\omega$ -3 polyunsaturated fatty acid, Glutamine, Arginine, Nucleotides, Taurine, Probiotics and many more. Use of these nutrients to hospitalised patients decrease the length of stay in hospitals and also infection rate. Glutamine has an essential nutrients for immune cells and important modulator of gut barrier function and it is also a substrate for glutathione synthesis. Thus it plays a pivotal role as an antioxidant thus has more specific effect on the function of lymphocytes. Arginine is an essential amino acids during growth and may become essential in catabolic state. It is the precursor for nitric acid (NO) which is important for immune function, thus it stimulates T-cell proliferation and activation.  $\omega$ -3PUFA has immunonutrient function due to their anti-inflammatory properties. In burn patient's it improves survival and reduces infection complication by decreasing the level of PGE2 in them. Taurine has role in membrane stabilization, osmoregulation and calcium influx regulation. Ganglionides have potent effects on cellular immune reactions. Even oat fibres and guar gum and pectin has shown to stimulate gastrointestinal associated lymphoid tissue and to protect the GI mucosa against oxidative damage. Many nutritional formulas are being developed which contain L-plantarum fermented oat fibre which pave the way for Immuno nutrients research to expand into new and exiting area.

**Keywords:** Immunonutrition,  $\omega$ -3 PUFA, Glutamine, Arginine, Taurine, Probiotics

## INTRODUCTION

The role of certain nutrients that seem to have pharmacologic effects on immune and inflammatory parameters has been studied over the last two decades.<sup>1</sup> Immunonutrition is defined as modulation of the activities of the immune activation by nutrients or specific food items fed in amounts above these normally encountered in the diet.<sup>1</sup>

Immunomodulatory substance interfere with 3 basic areas of the immune responses directly or indirectly; (i) the mucosal barrier function (ii) the cellular defence function and (iii) the local or systemic inflammatory response.<sup>2</sup>

At present there are a relatively limited number of nutrients employed in immunonutrients like:<sup>3</sup> n-3 polyunsaturated—Act as anti-inflammatory agents, Fatty Acid reverses immunosuppression

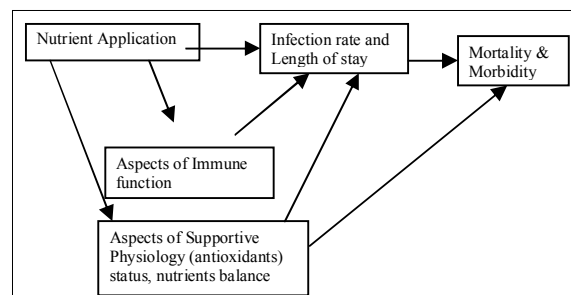
Glutamine—Nutrient for immune cell improve gut Barrier function, act a as a precursor for Glutathione  
Arginine—Substrate for NO synthesis, stimulates Growth hormone synthesis, improve T<sub>H</sub> Cell number  
Nucleotides—RNA & DNA precursors, improve T cell Function

The list of possible immunonutrients is ever expanding like addition of phospholipids, Taurine, Probiotics and medium chain Triglycerides in the sequence.<sup>4,5</sup>

Meta-analysis of clinical trials have shown improvement such as reduced risk of infection, fewer

days on a ventilator, and reduced length of intensive care unit and hospital stay.<sup>6</sup>

Improvement in out come was only seen when critical amount of the immune modulating formula were tolerated in patients classified as being malnourished. However, in other patients with sever sepsis shock and organ failure, no benefit or ever disadvantages from immunonutrition were reported. In such severe conditions we hypothesise that systemic inflammation might be undesirably intensified by Arginine and Unsaturated fatty acids directly affecting cellular defence and inflammatory response.<sup>6</sup>



**Key areas which are influenced by immunonutrition**

**Glutamine**

A number of roles have been ascribed to glutamine as an immunonutrient like:

- (i) as an essential nutrient for immune cells.
- (ii) an important modulator of gut barrier function.

(iii) as a substrate for glutathione synthesis

Glutathione plays a pivotal role as it acts directly as an antioxidant and maintains other components of defence in a reduced state. It has more specific effect on the function of lymphocytes via the thioredoxin system.<sup>3</sup>

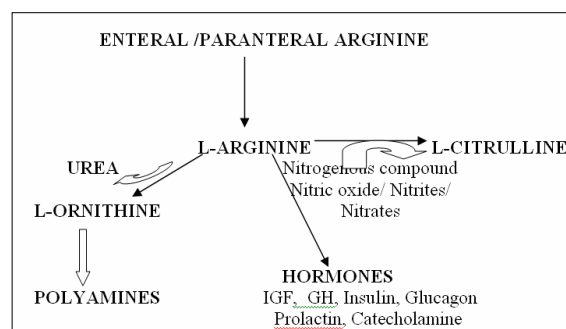
Glutamine constitutes 60% of free intracellular amino acids in skeletal muscles.<sup>7</sup> It is also principal metabolic fuel of gut mucosal cell<sup>8</sup>, lymphocytes and monocytes.<sup>9</sup> If adequate dietary glutamine is not provided to body during illness, the net catabolism of skeletal muscle will occur to supply the requirement of glutamine dependent tissue thus plasma and muscle glutamine concentration decreases in catabolic states.<sup>10</sup> Injury, infection, nutritional status and acute exercise can all influence plasma glutamine level these factors must be controlled and/or taken into consideration if plasma glutamine is to prove a useful marker of impending overtraining. Normal range of plasma glutamine level is 500 to 750  $\mu\text{mol/L}$  after an overnight fasting.<sup>11</sup> This level has been reported to fall in patients with untreated Diabetes mellitus, in diet- induced metabolic acidosis and in the recovery period following high intensity intermittent exercise. Common factors among all these stress states are rise in the plasma concentration of cortisol and glucagon and an increase for gluconeogenesis.

It is suggested that increased gluconeogenesis and associated increases in hepatic gut and renal glutamine uptake account for the depletion of plasma glutamine in catabolic stress state, including prolonged exercise.<sup>11</sup> Glutamine as such cannot be used in enteral food as it gets destroyed to ammonia and pyroglutamic acid so this problem overcomes by the use of Glutamine dipeptides which are soluble in small volume.<sup>10</sup> Glutamine has potential utility as a dietary supplement for athletes engaged in heavy exercise training.<sup>12</sup>

### Arginine

Arginine is an essential amino acid during growth and may become essential in catabolic state. It is the precursor for nitric acid (NO) which is a ubiquitous cellular messenger and is important for immune function. Patients receiving arginine supplemented feeding also had increased IGF-1 concentration and improved nitrogen balance.<sup>13</sup>

Arginine also improves macrophage and Natural killer cell tumour cytotoxicity; it increases leukocyte bacterial activity and the production of NO acts as a relaxing factor which acts as a potent vasodilator promoting wound healing. Furthermore, arginine stimulates T-cell proliferation and activation; it not only modulates nitrogen balance but also protein synthesis and cytokine production.<sup>14</sup>



### Role of Arginine

Arginine acts in the healing process by promoting collagen synthesis.<sup>15</sup>

### $\omega$ -3 PUFA

It has an immunonutrient function due to their anti-inflammatory properties. Perioperative feeding of colo-rectal cancer patients with arginine enriched enteral feed containing  $\omega$ -3PUFA resulted in a decrease in the postoperative rise in IL-6 and IL-1 soluble receptors and an increase in IL-2 receptor  $\alpha$ , an improvement in infection rate.<sup>3</sup> IL-6, IL1 and TNF- $\alpha$  are initiated by secretion of pro-inflammatory response which are:

- creation of hostile environment (for Pathogens)
- provision of nutrients for the immune system from endogenous sources
- strengthening of the protective and control system against response.

Inhibitory system comes into play to terminate the response to defeating pathogens. The control system is anti-inflammatory cytokines (e.g., IL-10), production of cytokine receptor antagonists (IL-1ra), secretion of glucocorticoids and down regulation of nuclear factor B activation by enhancement of antioxidant Defence.<sup>3</sup>

Diet rich in  $\omega$ -3PUFA's there is suppression in the production of a number of dienoic eicosanoid metabolites with increased production of trienoic metabolites which have low biological potency. If important PGE<sub>2</sub> is replaced by PGE<sub>3</sub>, TxA<sub>2</sub> by TxA<sub>3</sub> and PGI<sub>2</sub> by PGI<sub>3</sub>. Thus by  $\omega$ -3PUFA feed there is suppression of PGE<sub>2</sub> which has immuno suppression and leucocyte suppression function. In burn patient  $\omega$ -3PUFA's improves survival and reduces infection complication by decreasing the level of PGE<sub>2</sub> in them.<sup>10</sup> Other than having positive role  $\omega$ -3PUFA is an immunonutrient with some negative role too due to decreasing the TxA<sub>2</sub> concentration. TxA<sub>2</sub> has an important role in the maintenance of vascular tone and in platelet aggregation. Thus high doses of  $\omega$ -3PUFA's can lead to vasodilatation and prolonged bleeding.<sup>16</sup>

This can also lead to generation of lipid peroxides and consumption of the natural free radical scavenger, Vitamin E. These produce cellular and tissue damage and thus exacerbate the pathological process associated with multi organ failure.

### Taurine

It is one of the most abundant amino acids in many cell types, where its role include membrane stabilization, osmoregulation and calcium influx regulation, even it's immuno modulator function was generated by the discovery of its antioxidant capacity and its ability to prime leucocytes and to regulate the release of pro-inflammatory cytokines.<sup>17</sup>

Taurine supplementation also conferred immune benefits by down regulating TNF- $\alpha$  release and unregulating antibacterial capacity, as assessed by peritoneal macrophage superoxide generation. In the neutrophil taurine is a potent modulator of myeloperoxidase as a key enzyme in the respiratory burst chain.<sup>18</sup>

### Others

The list of possible immunonutrients is ever expanding. Many of the components of cellular membranes grouped together as phospholipids may also have immuno stimulatory effects. Phosphatidyl choline and Phosphatidyl inositol have been shown to reduce bacterial translocation in vivo after 90% liver resection.<sup>4</sup> Gangliosides may have potent effects on cellular immune reactions. The health benefits of fibre are by now well established even soluble fibre has been particularly studied in relation to its cholesterol-lowering capacity, and it has recently been exploited for its gastrointestinal trophic effect.<sup>4</sup> In particular, pectin has been shown to stimulate gastrointestinal associated lymphoid tissue and to protect the gastrointestinal mucosa against oxidative damage.<sup>4</sup> The benefit of oat fiber and guar gum are described as being similar to those of pectin.<sup>4</sup>

Probiotics are 'live microorganisms', which when administered inadequate amounts, confer a health benefit on the host. It stimulates immune system and is also one of the type of immuno nutrient.<sup>19</sup> It enhances the immune system by favourably altering the gut microecology and preventing unfriendly organisms from gaining a foothold in the body. They prevent the overgrowth of yeast and fungus and produces substances that can lower cholesterol.<sup>20</sup> The use of medium chain Triglycerides instead of total dependence on long chain triglycerides in supplemental feeds is proving beneficial in providing a safe, calorically rich nutrients and a source of essential fatty chain. Medium chain triglyceride to the feeding regimen achieves a progressive increase in lymphocytes

count, a decrease in serum aspartate transaminase and a significant improvement in Nitrogen balance.<sup>5</sup>

Dietary RNA may be necessary to maintain normal immune function. Nucleotides increases protein synthesis and are involved in regulation of several T cell mediated immune response.<sup>21</sup> Dietary nucleotide restriction has been shown to cause immunodepressive effects, documented by decreased lymphocyte mitogenesis and response to allogeneic antigens; by delay of the hypersensitivity response and by prolonged allograft survival.<sup>14</sup>

Zinc is other immunonutrients which play important role in maintenance of immune function in promotion of wound healing and in maintenance of intestinal mucosal integrity.<sup>22</sup>

Currently, a nutrition formula is being developed which contains L-plantarum fermented oat fibre. Development of such formulas will pave the way for immunonutrition research to expand into new and exciting areas.

### REFERENCES

1. Alvarez W, Mobarhan S. Finding a place for immuno nutrition. *Nutr Rev* 2003;61(6Pt.1):214-8.
2. Suchner U, Senfleben U, Felbinger TW. "Immune function and organ failure, immunomodulation with nutritional support—an update." *Anaesthesist* 2000;49:460-5.
3. Grimble RF. Nutritional modulation of immune function. *Proceeding of Symposium on "Evidence- based nutrition" Nutrition Society* 2001;60:389-97.
4. O'Flaherty L, David JBH. Immunonutrition and surgical practices. *Proc Nutr Soc* 1999;58:831-7.
5. Baqain ZH. Nutritional Support in Oral Cancer patients: An updated review. *Saudi Dent J* 2004;16(3):122-7.
6. Suchner U, Kuhn S, Furst P. The scientific basis of immunonutrition. *Proc Nutr Soc* 2000;59(4):553-63.
7. Roth E, Funovics J, Muhlbacher F, Schemper M, Mauritz W, Sporn P, *et al*. Metabolic disorders in severe abdominal sepsis; glutamine deficiency in skeletal muscles. *Clin Nutr* 1982;1(1):25-41.
8. Souba WW, Klimberg VS, Plumley DA, Salloum RM, Flynn TC, Bland KI, *et al*. The role of glutamine in maintaining a healthy gut and supporting the metabolic response to injury and infection. *J Surg Res* 1990; 48:383-91.
9. Madden HP, Breslin RJ, Wasserkrug HL, Efron G, Barbul A. Stimulation of T-cell immunity by enhances survival in peritonitis. *J Surg Res* 1988;44:658-63.
10. O'leary MJ, Coakley JH. Nutrition and Immunonutrition. *Br J Anaesth* 1996;77:118-27.
11. Walsh NP, Blannis AK, Robson PJ, Gleeson M. Glutamine, exercise and immune function. Links and possible mechanism. *Sports Med* 1998;26(3):177-91.
12. Antonio J, Street C. Glutamine: a potentially useful supplement for athletes. *Can J Appl Physiol* 1999;24(1):1-14.
13. Madden HP, Breslin RJ, Wasserkrug HL. Stimulation of T-cell immunity by arginine enhances survival in peritonitis. *J Surg Res* 1988;44:658-63.
14. Lorenzo D, Rover F, Pericelli A, Imperatori A. The rationale of early enteral nutrition. *Acta Bio Medica* 2003;74(Suppl 2):41-4.
15. Lebuffe G. Recent clinical and medical economic studies. *J Chir (Paris)* 2008;145(Suppl 4):956-9.

16. Peck MD. Omega-3 polyunsaturated fatty acid: benefit or harm during sepsis. *New Horiz* 1994;2:230-6.
  17. Gordon RE, Shaked AA, Salono DF. Taurine protects hamster bronchioles from acute NO<sub>2</sub> induced alteration. *Am J Pathol* 1986;125:585-600
  18. O'Flaherty L, Stapleton PP, Redmond HP, Bouchier HDJ. Taurine modulates immune response and reduces bacterial translocation and gut atrophy in a murine model of sepsis. *Proc Nutr Soc* 1998;57:143A
  19. Suvarna VC, Bobby VU. Probiotics in Human health: A current assessment. *Curr Sci* 2005;88:1744-7.
  20. <http://www.healingdaily.com>
  21. Carver JD, Cox WI, Barnes LA. Dietary nucleotide effects upon murine natural killer cell activity and macrophage activation. *JPEN J Parenter Enteral Nutr* 1990;14:18-22.
  22. Jeejeebhoy K. Nutrient requirements and nutrient deficiencies in gastrointestinal diseases. In: Sleisenger M, Fordtran J, Feldman M (eds). *Gastrointestinal Diseases: Pathophysiology Diagnostic Management*, 5<sup>th</sup> ed. Philadelphia: WB Saunders; 1993.p. 2017-47.
- 

**Address for Correspondence:**

**Dr. Puja Dullo**, III/10, Medical College Campus, Govt. Medical College, Kota, Rajasthan, India 324005.

**Email:** [puja\\_dullo@yahoo.com](mailto:puja_dullo@yahoo.com)